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PRINCIPAL INVESTIGATOR: Beatrice Knudsen, M.D., Ph.D.

CONTRACTING ORGANIZATION: Fred Hutchinson Cancer Research Center
Seattle WA 98109-1024

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Beatrice Knudsen, M.D., Ph.D.

E-Mail: bknudsen@fhcrc.org

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14. ABSTRACT

In this project we plan to analyze andron-and estrogen-responsive gene expression in the bone marrow. We plan to work to: determine if castration-induced gene expression changes in mouse bone marrow are cause by the deficiency of testosterone or estrogen; analyze androgen-and estrogen-sensitive cytokine and gene expression changes in human bone marrow transplanted into NOD/SCID mice, and; examine androgen-and estrogen-sensitive gene expression in the bone marrow of patients with low and high circulating testosterone levels.
This research project was delayed as a result of second-level review required by the US Army Medical Research Materiel Command's Human Subjects Research Review Board (HSRRB). Final approval from the HSRRB was received on November 21, 2006. We are now organizing the animal work and obtaining human samples of bone marrow from patients with prostate cancer for analysis.

15. SUBJECT TERMS
Bone marrow metastasis, androgen, animal model, patient outcome

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SUBJECT: Annual Report for Contract Number W81XWH-06-1-0171

"Androgen, Estrogen, and the Bone Marrow Microenvironment"

INTRODUCTION:
In this project we plan to analyze androgen- and estrogen-responsive gene expression in the bone marrow. We postulate that gene and protein expression in the bone marrow microenvironment is subject to regulation by androgen and estrogen and could affect the growth and progression of micrometastatic prostate cancer cells. When prostate cancer cells leave the circulation through fenestrations in the bone vasculature, they lodge in the fertile soil of the bone marrow. Interactions between prostate cancer cells and the bone marrow regulate the early steps of metastasis formation. This environment differs from the environment of established prostate cancer metastasis, in which a fibrotic bone marrow stroma surrounds the cancer cells and cancer cells stimulate an osteoblastic response in adjacent bone. Almost nothing is known about the initial interactions of micrometastatic prostate cancer with the bone marrow microenvironment (BM-ME). During this period critical decisions in the fate of micrometastatic cancer cells occur that determine their latency, survival and proliferation. Most likely, factors in the BM-ME play a major role in regulating the progression of micrometastatic disease. While model systems exist for several steps in metastasis formation, including interactions of prostate cancer cells with endothelial cells and osteoblastic and osteoclastic bone cells, there is no *in-vivo* system to investigate the interactions between prostate cancer cells and the BM-ME. Therefore, there are many unanswered questions related to events that will ultimately determine who develops lethal prostate cancer metastases. In this grant application we will begin to investigate mechanisms that control the fate of prostate cancer cells when they first enter the BM.

Early androgen ablation has a significant survival benefit in patients at risk for prostate cancer recurrence or with increasing PSA levels after surgery or radiation therapy. At the initiation of androgen ablative therapy, the disease is often not apparent by conventional radiographic methods. However, the majority of patients will have micrometastatic disease outside the prostate. Therefore it is important to understand if and how androgen ablative therapy affects the bone marrow cells that surround the micrometastatic cancer cells. In this study, we plan to work to: determine if castration-induced gene expression changes in mouse bone marrow are caused by the deficiency of testosterone or estrogen; analyze androgen- and estrogen-sensitive cytokine and gene expression changes in human bone marrow transplanted into NOD/SCID mice, and; examine androgen- and estrogen-sensitive gene expression in the bone marrow of patients with low and high circulating testosterone levels.

BODY:
This research project was subject to second-level review by the U.S. Army Medical Research Material Command's Human Subjects Research Review Board (HSRRB). Because of this review, study implementation was precluded until we met specific requirements for compliance with human subjects protection and received approval from our local IRB and then the HSRRB. We received final approval from the HSRRB on November 21, 2006.

KEY RESEARCH ACCOMPLISHMENTS:
We are organizing the animal work and obtaining human samples of bone marrow from patients with prostate cancer that we are analyzing.

REPORTABLE OUTCOMES:
At this time, there are no reportable outcomes.

CONCLUSIONS:
N/A

REFERENCES:

None